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May 17, 2004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of R. Sandeman, D. Chandler, A. Duncan, and P. Hay
Application No. 10/674,196 — Group No. 1625
Filed September 29, 2003 — Examiner Not Yet Assigned
Insecticide and Method of Controlling Insects

(Atty. Docket No. P27,299 USA)

CERTIFICATE OF MAILING

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Sir:

Forwarded herewith is a certified copy of Australian Application No. PR4069, filed March 29, 2001. This is the priority document for the present application.

Respectfully submitted,

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I, JULIE BILLINGSLEY, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. PR 4069 for a patent by NUFARM LIMITED and LA TROBE UNIVERSITY as filed on 29 March 2001.

WITNESS my hand this
Twenty-third day of April 2004

J. Billingsley

JULIE BILLINGSLEY
TEAM LEADER EXAMINATION
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AUSTRALIA
Patents Act 1990

PROVISIONAL SPECIFICATION

Invention Title: INSECTICIDE AND METHOD OF CONTROLLING INSECTS

Applicant: **NUFARM LIMITED and LA TROBE UNIVERSITY**

The invention is described in the following statement:

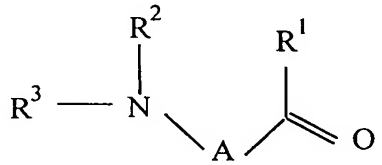
Insecticide and Method of Controlling Insects

The invention relates to insecticidal compounds and compositions for controlling insecticides and to a method of controlling insects using the insecticidal compounds and compositions.

Insecticides are chemicals that are used to control damage or annoyance from insects. Control of insects may be achieved by oral ingestion of stomach poisons, contact poisons that penetrate the cuticle or fumigants that penetrate the respiratory system.

The wide use of insecticides particularly in crop protection has lead to the emergence of resistant insects. There is a need for new types of insecticides which are safe to use.

The invention provides an insecticidal compound of Formula I



I

and the agriculturally acceptable salts thereof,
wherein:

R^1 is selected from the group consisting of
hydroxyl;
the group OR^5 wherein R^5 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic and substituted heterocyclic;
the group $-NR_6OH$ wherein R^6 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, carbocyclic and substituted carbocyclic;
the group NR^7R^8 wherein R^7 and R^8 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl and carbocyclic; and

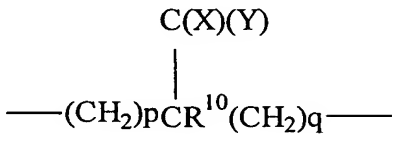
the group wherein R^1 is linked to R^2 to form a diradical bridging group;

R^2 and R^3 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, carbocyclic, substituted carbocyclic, aryl, substituted aryl, acyl and substituted acyl; and

A is a diradical linking group which has a molecular weight of preferably less than 200 and more preferably less than 100.

The compounds include the agriculturally acceptable salts of compounds of formula I such as the salts formed at the amine moiety, phosphonic acid moiety carboxylic acid moiety and mixtures thereof.

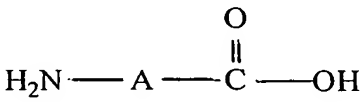
A is preferably a diradical group of formula



wherein the groups R^{10}, X and Y are independently selected from the group consisting of hydrogen, alkyl, thiol, hydroxy, thioalkyl, alkoxy, substituted alkyl, carboxyclic, substituted carboxyclic, heterocyclic and substituted heterocyclic; and

p and q are selected from zero, 1, 2 and 3.

A may be a group wherein the formula



is a naturally occurring amino acid.

Preferred A is selected from the group wherein R^{10} is hydrogen, p and q are zero and X and Y are as defined above.

In more the preferred A group X is selected from the group consisting of hydrogen and C_1 to C_6 alkyl and Y is selected from the group consisting of hydrogen, C_1 to C_6 alkyl and phenyl.

It is preferred that the substituent R^1 is selected from the group consisting of hydroxy;
the group OR^5 wherein R^5 is selected from the group consisting of hydrogen, alkyl, haloalkyl, aryl substituted alkyl, heterocyclic, heterocyclic substituted with alkyl wherein the alkyl is optionally further substituted with hydrocarbyloxy;
the group NR^7R^8 wherein R^7 and R^8 are independently selected from hydrogen and C_1 to C_6 alkyl; and
the group wherein R^1 is linked to R^2 to form a bridging group $-R^2 \cdot R^1-$ of formula

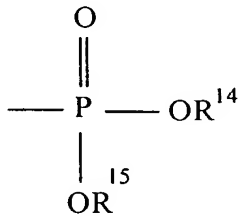
$$-(CR^{12}R^{13})_nO_q-;$$

wherein n is 1 or 2, q is zero or 1 and R^{12} and R^{13} are independently selected from hydrogen, halogen, alkyl and haloalkyl.

More preferred R^1 is selected from the group consisting of
hydroxy;
the group OR^5 wherein R^5 is selected from the group consisting of hydrogen, alkyl, haloalkyl, aralkyl and alkylaryl and wherein more preferred R^5 is hydrogen, C_1 to C_6 alkyl, halogenated C_1 to C_4 alkyl;
the group NR^6OH wherein R^6 is selected from hydrogen and alkyl, preferably from hydrogen and C_1 to C_4 alkyl and most preferably hydrogen;
the group NR^7R^8 wherein R^7 and R^8 are independently selected from hydrogen and C_1 to C_4 alkyl.

The preferred group R^2 is selected from the group consisting of hydrogen, alkyl,, haloalkyl, aryl, alkylaryl and aralkyl;

the group substituted alkyl, substituted haloalkyl, substituted acyl, substituted aryl, substituted alkylaryl and substituted arylalkyl, wherein the subsitutuent is a group of formula



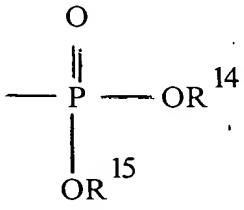
wherein R^{14} and R^{15} are independently selected from the group consisting of hydrogen, halo, alkyl, aryl, alkanoyl, aralkyl, haloalkyl, haloaryl, haloalkyl aryl and haloarylalkyl; and

the group wherein R^2 is linked to R^1 to provide the group $-R^2-R^1-$ of formula

$$-(CR^{12}R^{13})_nO_p-$$

wherein n is 1 or 2, p is O or 1 and R^{12} and R^{13} are independently selected from hydrogen, alkyl and haloalkyl.

More preferably R^2 is selected from the group consisting of hydrogen C_1 to C_8 alkyl halo $-(C_1$ to $C_6)$ alkyl and C_1 to C_6 alkyl substituted by the group of formula



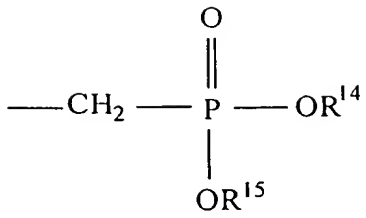
wherein R^{14} and R^{15} are independently selected from the group consisting of hydrogen and C_1 to C_4 alkyl; and

and the group wherein R^2 is linked to R^1 to provide the group $-R^1 \cdot R^2-$ of formula

$$-(CR^{12}R^{13})O-$$

where R^{12} and R^{13} are independently selected from hydrogen, C_1 to C_4 alkyl and C_1 to C_4 haloalkyl.

Even more preferred R^2 is selected from the group consisting of hydrogen; and C_1 to C_4 alkyl; the group of formula

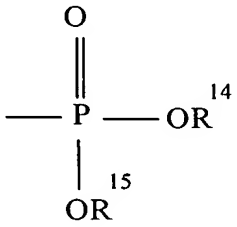


wherein R^{14} and R^{15} are independently selected from the group consisting of hydrogen and C_1 to C_4 alkyl; and the group wherein R^2 is linked to R^1 to provide the group $-R^2-R^1-$ of formula

$$-(CR^{12}R^{13})O-$$

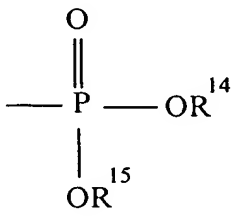
wherein R^{12} and R^{13} are selected from methyl and trifluoromethyl.

Preferably the substituent R^3 is selected from the group consisting of hydrogen, alkyl; haloalkyl; aryl; acyl; alkoxycarbonyl-substituted acyl; alkylaryl; aralkyl; and the groups substituted alkyl, substituted haloalkyl, substituted acyl, substituted alkaryl and substituted aralkyl wherein the substituent is the group of formula



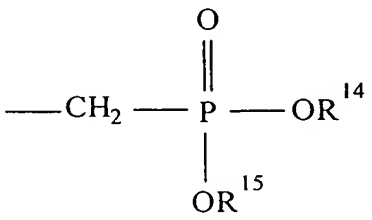
wherein R^{14} and R^{15} are independently selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, alkylaryl, haloalkyl, haloaryl haloalkylaryl and haloaralkyl.

More preferably the substituent R^3 is selected from the group consisting of hydrogen, C_1 to C_6 alkyl, C_1 to C_6 alkanoyl, C_1 to C_6 haloalkyl and C_1 to C_6 alkyl and C_1 to C_6 alkyl substituted by the group of formula



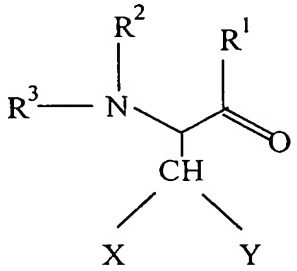
wherein R^{14} and R^{15} are independently selected from the group consisting of hydrogen and C_1 to C_4 alkyl.

Even more preferably the substituent R^3 is selected from the group consisting of hydrogen, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl, C_1 to C_4 alkanoyl and the group of formula



wherein R^{14} and R^{15} are selected from the groups consisting of hydrogen and C_1 to C_4 alkyl.

In a particularly preferred embodiment the compounds of the invention are of formula Ia

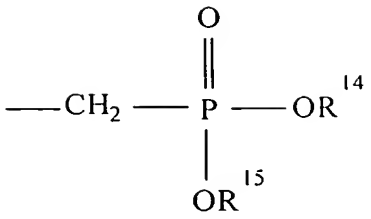


Ia

wherein R^1, R^2 and R^3 are as hereinbefore defined and X and Y are independently selected from the group consisting of hydrogen, thiol, alkyl, haloalkyl, aryl, acyl, aralkyl, heterocyclic and heterocyclicalkyl.

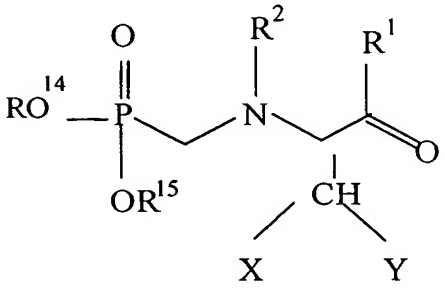
The preferred groups X and Y are independently selected from hydrogen, C_1 to C_4 alkyl, aryl, arylalkyl and heterocyclic.

We have found that compounds of formula Ia are particular insecticidally active where at least one of R^2 and R^3 is a group of formula



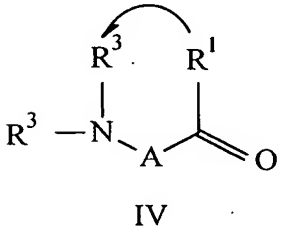
wherein R^{14} and R^{15} are as hereinbefore defined.

Specific examples of such compounds include compounds of formula III

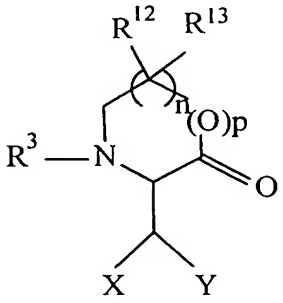


III

In one embodiment of the compounds of formula I the groups R^1 and R^2 are linked together to form a diradical linking group $-R^2-R^1-$. Such compound preferably have the formula IV and preferred examples of such compounds are of formula IVa



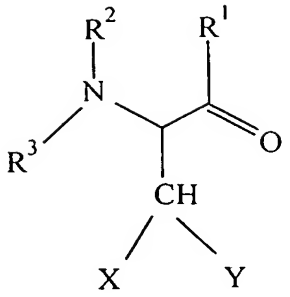
IV



IV

hereinbefore defined.

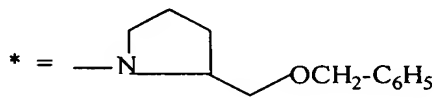
Specific examples of the compounds of formula Ia are shown in Table 1 below:



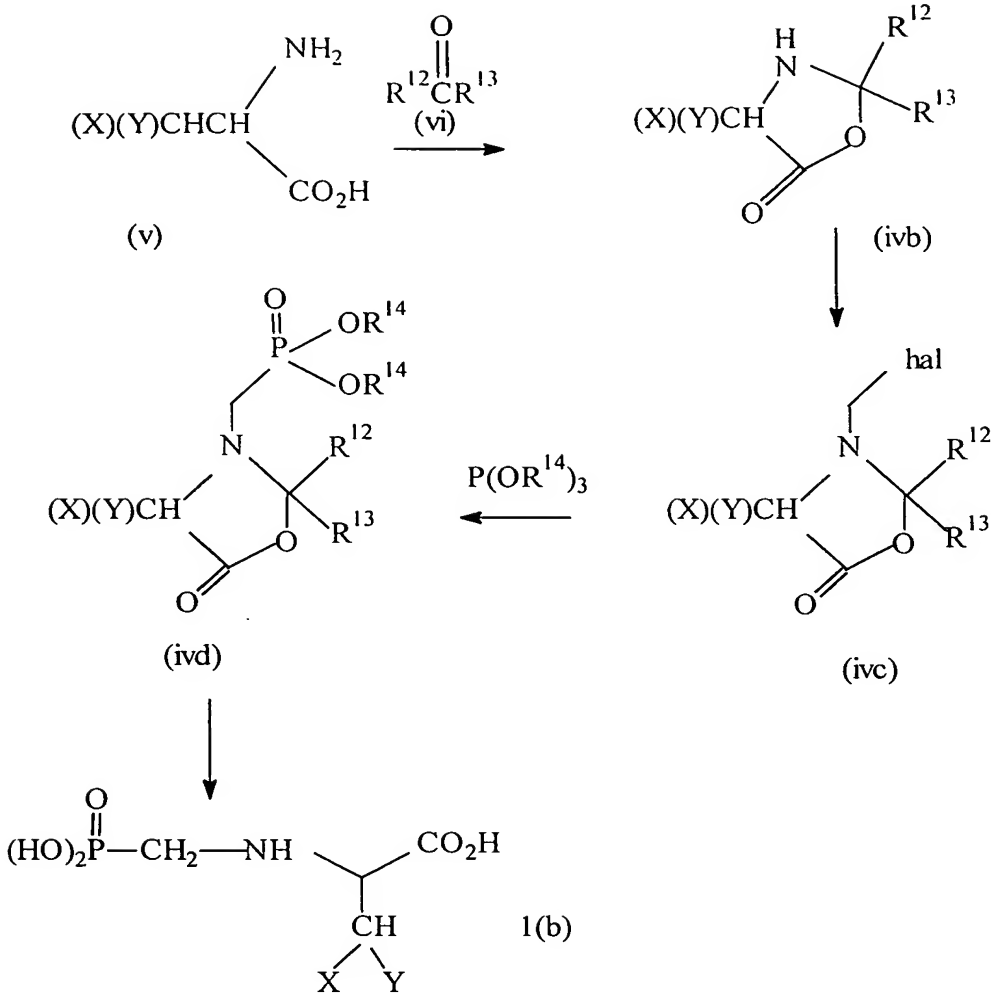
Ia

Table 1

	R^1	R^2	R^3	X, Y
1.	OH	H	$CH2PO(OH)_2$	CH_3, CH_3
2.	NHOH	H	$CH_2PO(OH)(OCH_3)$	$CH(CH_3)_2$, H
3.	NHOH	H	$CH_2PO(OH)(OCH_3)$	C_6H_5, H
4.	OH	H	CH_3	H, H
5.	OH	H	$CH_2PO(OH)_2$	C_6H_5, H
6.	NHOH	H	CH_3	H, H
7.	NHOH	H	$CH_2PO(OH)(OCH_3)$	H, H
8.		$-OC(CF_3)_2-$	$CH_2PO(OCH_3)_2$	$-CH(CH_3)_2$, H
9.	NHOH	H	CH_3CO-	CH_3, OH
10.	OCH_3	H	$CH_2PO(OCH_3)_2$	C_6H_5, H
11.		$-OC(CF_3)_2-$	$BrCH_2-$	C_6H_5, H
12.	OCH_3	$CH_2PO(OCH_3)_2$	$CH_2PO(OCH_3)_2$	CH_3, CH_3
13.		$-OC(CF_3)_2-$	CH_3	C_6H_5, H
14.	NHOH	H	$CH_2PO(OH)_2$	CH_3, CH_3
15.	OH	H	CH_3	CH_3, CH_2CH_3
16.	NHOH	H	$CH_2PO(OH)_2$	H, $CH(CH_3)_2$
17	*	H	H	CH_3, CH_3



The insecticidal compounds of the invention may be prepared by a range of methods. In a preferred aspect the compounds of formula I and having specific formula ivb, ivc, ivd or ib are prepared according to scheme 1 below:



Scheme 1

Further compounds of formula 1 may be prepared from the compounds of formula (ivb), (ivc), (ivd) and 1(b) by suitable methods.

In a preferred aspect the preferred compounds are prepared by reaction of an amino acid of formula (v) with a ketone of formula (vi) to provide a compound of formula (ivb); reaction of the compound of formula (ivb) with paraformaldehyde in the presence of a halogen particularly bromine to provide a compound of formula (ivc) wherein hal is halogen (preferably bromine); reacting the compound of formula (ivc) with a phosphite to provide a phosphonate ester of formula (ivd) and hydrolysis, preferably in aqueous acid, to provide the compound of formula 1(b).

Preferred salts of compounds of formula I are salts formed with cations selected from the group consisting of alkali metals, alkaline earth metals, copper, zinc, manganese, nickel, ammonium, organic ammonium, organic sulphonium, and mixtures thereof. The most preferred salts are those in which at least one of the groups R^5, R^{14} and R^{15} is a counter ion and the others are hydrogen.

Examples of organic ammonium may be selected from the group consisting of monoalkylammonium, dialkylammonium, trialkylammonium, monoalkenyl-ammonium, dialkenylammonium, trialkenylammonium, monoalkanolammonium, dialkanolammonium, trialkenolammonium, heterocylicammonium and aryl-ammonium. The preferred alkyl and alkenyl groups contain one to four carbon atoms.

The preferred salts are selected from the group consisting of alkali metals, alkaline earth metals, ammonium, alkyl ammonium (particularly isopropyl ammonium), trimesium and mixtures thereof.

Specific examples of the salt preferred compounds of the invention include: N-phosphonomethylvaline, sodium salt of N-phosphonomethylvaline, ammonium salt of N-phosphonomethylvaline, isopropylammonium salt of N-phosphonomethylvaline, trimesium salt of N-phosphonomethylvaline, N-phosphonomethylleucine, sodium salt of N-phosphonomethylleucine, ammonium salt of N-phosphonomethylleucine, trimesium salt of N-phosphomethylleucine.

The compounds of Formula Ia, III and IV include at least one chiral centre at the α carbon atom (ie the carbon atom α to the carboxyl or carboxylate group). The compounds of the invention may be in the form of the L-enantiomer the D-enantiomer or racemic mixtures thereof. In one embodiment the compound of Formula I is comprised of at least 80% of one enantiomer and preferably at least 90% of one enantiomer.

In a further embodiment the invention provides an insecticidal composition comprising one or more compounds of Formula I and an agriculturally acceptable carrier.

The insecticidally effective carrier may be any of the carriers known in the art and may provide a solid granular product, an aqueous solution or an emulsion containing the active component.

The compounds of formula I may be applied directly to insects or the locus of insects such as plants to be protected or soil.

The compounds of formula I may be used on their own to kill insects, inhibit the growth of insects or reduce the damage caused by insects but are preferably used in the form of a composition comprising a compound of the invention in admixture with a carrier comprising a solid or liquid diluent. Therefore, in yet a further aspect the invention provides an insecticidal compound as hereinbefore defined and carrier therefor.

The compositions of the present invention may be in the form of solids, liquids or pastes. The compositions include both dilute compositions which are ready for immediate use and concentrated compositions which may require dilution before use. Therefore, the concentration of the active ingredient in the compositions of the present invention will vary depending on the type of formulation and whether the composition is ready for use such as, for example, a dust formulation or an aqueous emulsion or whether the composition is a concentrate such as, for example, an emulsifying concentrate or a wettable powder, which is suitable for dilution before use. In general the compositions of the present invention comprise from 1 ppm to 99% by weight of active ingredient.

The solid compositions may be in the form of powders, dusts, pellets, grains, and granules wherein the active ingredient is mixed with a solid diluent. Powders and dusts may be prepared by mixing or grinding the active ingredient with a solid carrier to give a finely divided composition. Granules, grains and

pellets may be prepared by bonding the active ingredient to a solid carrier, for example by coating or impregnating the preformed granular solid carrier with the active ingredient or by agglomeration techniques.

Examples of solid carriers include mineral earths and clays such as, for example, kaolin, bentonite, kiesulguhr, Fuller's earth, Attaclay, diatomaceous earth, hole, loess, talc, chalk, dolomite, limestone, lime, calcium carbonate, powdered magnesia, magnesium oxide, magnesium sulfate, gypsum, calcium sulfate, prophyllite, silicic acid, silicates and silica gels; fertilizers such as, for example, ammonium sulfate, ammonium phosphate, ammonium nitrate and urea, natural products of vegetable origin such as, for example, grain means and flours, bark meals, wood meals, nutshell meals and cellulosic powders; and synthetic polymeric materials such as, for example, ground or powdered plastics and resins.

Alternatively, the solid compositions may be in the form of water soluble or water dispersible dusts, powders, granules or grains wherein the active ingredient and the solid carrier are combined with one or more surface active agents which act as wetting, emulsifying and/or dispersing agents to facilitate the dispersion or solubilisation of the active ingredient in liquid.

Examples of surface active agents include those of the cationic, anionic and non-ionic type. Cationic surface active agents include quaternary ammonium compounds, for example, the long chain alkylammonium salts, such as cetyltrimethylammonium bromide. Anionic surface active agents include: soaps or the alkali metal, alkaline earth metal and ammonium salts of fatty acids; the alkali metal, alkaline earth metal and ammonium salts of ligninsulfonic acid; the alkali metal, alkaline earth metal and ammonium salts of arylsulfonic acids including the salts of naphthalenesulfonic acids such as butylnaphthalenesulfonic acid, and di- and tri-isopropylnaphthalenesulfonic acids, the salts of the condensation products of sulfonated naphthalene and naphthalene derivatives with phenol and formaldehyde, and the salts of alkylarylbenzenesulfonic acids such as dodecylbenzenesulfonic acid; the alkali metal, alkaline earth metal and ammonium salts of the long chain mono esters

of sulfuric acid or alkylsulfates such as laurylsulfate and the monoesters of sulfuric acid with fatty alcohol glycol ethers. Nonionic surface active agents include: the condensation products of ethylene oxide with fatty alcohols such as oleyl alcohol and cetyl alcohol; the condensation products of ethylene oxide with phenols and alkylphenols such as isooctylphenyl, octylphenol and nonylphenol; the condensation products of ethylene oxide with castor oil; alkyl polyglycoside surfactants; the partial esters derived from long chain fatty acids and hexitol anhydrides, for example sorbitan monolaurate, and their condensation products with ethylene oxide; ethylene oxide/propylene oxide block copolymers; lauryl alcohol polyglycol ether acetal; and lecithins.

The liquid compositions may comprise a solution or dispersion of the active ingredient in a liquid carrier optionally containing one or more surface active agents which act as wetting, emulsifying and/or dispersing agents. Examples of liquid carriers include: water, mineral oil fractions such as, for example, kerosene, solvent naphtha, petroleum, coal tar oils and aromatic hydrocarbons such as, for example, paraffin, cyclohexane, toluene, the xylenes, tetrahydronaphthalene and alkylated naphthalenes; alcohols such as, for example, methanol, ethanol, propanol, isopropanol, butanol, cyclohexanol and propylene glycol; ketones such as, for example, cyclohexanone and isophorone; and strongly polar organic solvents such as, for example, dimethylformamide, dimethylsulfonoxide, N-methylpyrrolidone and sulfolane.

A preferred liquid composition comprises an aqueous suspension, dispersion or emulsion of the active ingredient which is suitable for application by spraying, atomising or watering. Such aqueous compositions are generally prepared by mixing concentrated compositions with water. Suitable concentrated compositions include emulsion concentrates, pastes, oil dispersions, aqueous suspensions and wettable powders. The concentrates are usually required to withstand storage to be capable of dilution with water to form aqueous preparations which remain homogenous for a sufficient time to enable them to be applied by conventional spray equipment. The concentrates conveniently contain from 20 to 80%, preferably 20 to 60% by weight of active ingredient.

Emulsion or emulsifiable concentrates are conveniently prepared by dissolving the active ingredient in an organic solvent containing one or more surface active agents. Pastes may be prepared by blending the finely divided active ingredient with a finely divided solid carrier, one or more surface active agents and optionally an oil. Oil dispersions may be prepared by grinding together the active ingredient, a hydrocarbon oil, and one or more surface active agents. Aqueous suspension concentrates may conveniently be prepared by ball milling a mixture of the active ingredient, water, at least one surface active agent and preferably at least one suspending agent. Suitable suspending agents include: hydrophilic colloids such as, for example, poly(N-vinylpyrrolidone), sodium carboxymethylcellulose and the vegetable gums gum acacia and gum tragacanth; hydrated colloidal mineral silicates such as, for example, montomorillonite, beidellite, nontronite, hectorite, saponite, sauconite and bentonite; other cellulose derivatives; and poly(vinyl alcohol). Wettable powder concentrates may conveniently be prepared by blending together the active ingredient, one or more surface active agents, one or more solid carriers and optionally one or more suspending agents and grinding the mixture to give a powder having the required particle size.

The aqueous suspensions, dispersions or emulsions may be prepared from the concentrated compositions by mixing the concentrated compositions with water optionally containing surface active agents and/or oils.

Preferred solid compositions use water dispersible granule formulations comprising the active ingredient together with a solid carrier, optionally containing one or more solid or liquid surfactant active agents and other herbicidal adjuvants known to the art. The water dispersible granules may be prepared using methods known to the art, such as the wet granulation method.

The mode of application of the compositions of the invention will depend to a large extent on the type of composition used and the equipment available for its application. Solid compositions may be applied by dusting or any other suitable means for broadcasting or spreading the solid. Liquid compositions may be

applied by spraying, atomising, watering, introduction into the irrigation water, or any other suitable means for broadcasting or spreading the liquid.

The compounds of the invention may be used in admixture with other insecticides to provide improved efficacy or more effective plant protection.

The invention further provides a method of controlling insects comprising applying to the insects or the locus of the insects an effective amount of the compound of Formula I.

The compounds of the invention are particularly effective in controlling insects in crops. Examples of pests on which the insecticide of the invention may be effective include: insect species of the orders Lepidoptera, Hemiptera, Orthoptera, Coleoptera, Psocoptera, Isoptera, Thysanoptera and Homoptera. These pests which cause massive losses to many horticultural and broadacre crops and stored and manufactured grain products. Other examples of insect pests which may be controlled may include Diptera, Anaplura, Malophaga and Siponaptera cause parasitic infections in animals and man and Hymenoptera, Dictyoptera, Isoptera which are domestic and industrial pests.

Accordingly in a preferred embodiment of the method of the invention we provide a method of plant protection comprising applying to the plants an insecticidal composition as hereinbefore described.

The insecticides of the invention are particularly effective in controlling Helicoverpa spp (Heliothis, cotton budworm) in cotton.

Although not wishing to be bound by theory we understand from our experimental results that some of the insecticides of the invention control insect populations by inhibition of aminopeptidases. Insect aminopeptidases conduct the terminal stage of protein digestion and facilitate uptake of amino acids or peptides across the wall of the mid-gut. They are also believed to act on all wall proteins during moulting and egg hatch. Some of the insecticides of the invention are therefore believed to enable control of insects via a mechanism

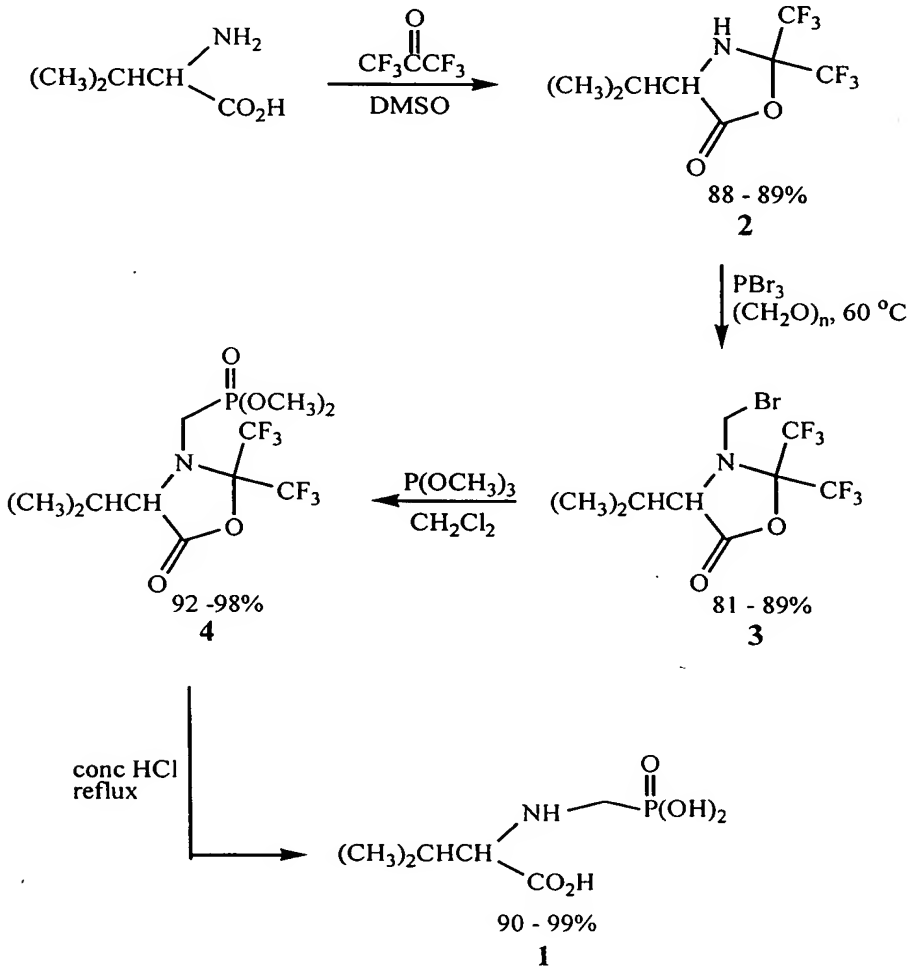
different to that of conventional insecticides and may provide a way to counteract the problem of insect resistance.

The invention will now be described with reference to the following examples. It is to be understood that the examples are provided by way of illustration of the invention and that they are in no way limiting to the scope of the invention.

Example 1

Preparation of N-Phosphonomethyl-L-Valine

N-Phosphonomethyl-L-Valine (see compound designated C1 in table below) is believed to be a new composition of matter, and was prepared according to Scheme 2 below.



Scheme 2. Synthesis of N-Phosphonomethyl-L-Valine

Other amino acids may be capable of similar derivatisation as valine in the above scheme.

The specific details of reaction in the synthesis of N-Phosphonomethyl-L-Valine were as follows (see also general reaction scheme which is provided above)

(a) Valine plus hexafluoroacetone

Hexafluoroacetone (10g) was bubbled into a suspension of (L)-Valine (4.0g, 34.1mmol) in DMSO (30mL) in a 2-necked round-bottomed flask equipped with a dry-ice condensor. Slight warming was necessary to prevent the DMSO from freezing. After a clear solution was obtained, excess hexafluoroacetone (2g) was bubbled into the reaction mixture, and stirring continued for 3-4h at ≈45°C (oil-bath temp). The excess hexafluoroacetone was distilled off into a water trap. The reaction mixture was poured into water (100mL) and extracted with CH_2Cl_2 (2 x 50mL). The combined organic extracts were washed with water (2 x 50mL) and dried over anhydrous Na_2SO_4. The mixture was distilled at atmospheric pressure to remove the CH_2Cl_2.

Yield : 8.02g (89%) – clear colourless liquid.

(b) Bromination

A mixture of valine trifluoromethyl oxazolidinone (8.0g, 30mmol), paraformaldehyde (1.81g) and phosphorus tribromide (6mL) was heated at 60 °C (oil-bath temp) for 2h.

The reaction mixture was distilled under vacuum (≈ 0.1mmHg)
Fraction1, 25-30 °C – PBr_3
Fraction 2, 40-50 °C – clear colorless liquid, 9.6g (89%)

(c) Phosphonate Ester Moiety

Trimethylphosphite (1.19mL, 10mmol, 1.2equiv) was added dropwise to a solution of valine-methylbromide (3.0g, 8.3mmol, 1equiv) and CH_2Cl_2

(5mL) at room temp. Stirring was continued for 1h. The reaction mixture was concentrated in vacuo, white solid, 3g (92%).

(d) Hydrolysis of Phosphonate Ester

A soln of the valine-methylphosphonate (2.0g, 5mmol) and concentrated HCl (6mL) was heated at reflux for 5h. The reaction mixture was concentrated in vacuo. The residue was dissolved in ethanol. Propylene oxide (2mL) was then added. A white solid precipitated. Ether (25mL) was then added, and stirring continued for 15min. The solid product was isolated by suction filtration, washed with ether and dried in vacuo. Yield 1.02g (93%) – white solid (semi-solid at room temp).

Examples 2 to 17

The compounds of examples 2 to 17 were prepared by a method in accordance with Example 1. The reagents were modified in accordance with the general procedure of scheme 1. Compounds 1 to 17 were subjected to bioassay in accordance with the following procedure and the results are shown in Table 2.

Helicoverpa colony maintenance

H. armigera were obtained from the CSIRO Entomology, Indooroopilly, QLD, Australia. *H. armigera* and *H. punctigera* were housed in independent constant temperature rooms (25-27šC) with a 16/8 hour light/dark cycle. Larvae were reared in individual cups containing 1.5cm cubes of media. Media comprised 234g Haricot beans, 14g agar, 35g Tortula yeast, 50g wheatgerm, 3.5g ascorbic acid, 1.1g sorbic acid and 2.2g p-hydroxybenzoic methylester made up to 1L with dH_2O, and was supplemented with 200mg penicillin, 200mg streptomycin and 16mg prochloraz. For every third generation of larvae raised, 50mg chloramphenicol was added to 1L of media. Care was taken during the rearing process to limit to potential for the development of contamination. To maintain viability, new larvae obtained from the field were added to the colony every third to fourth generation.

Media bioassay

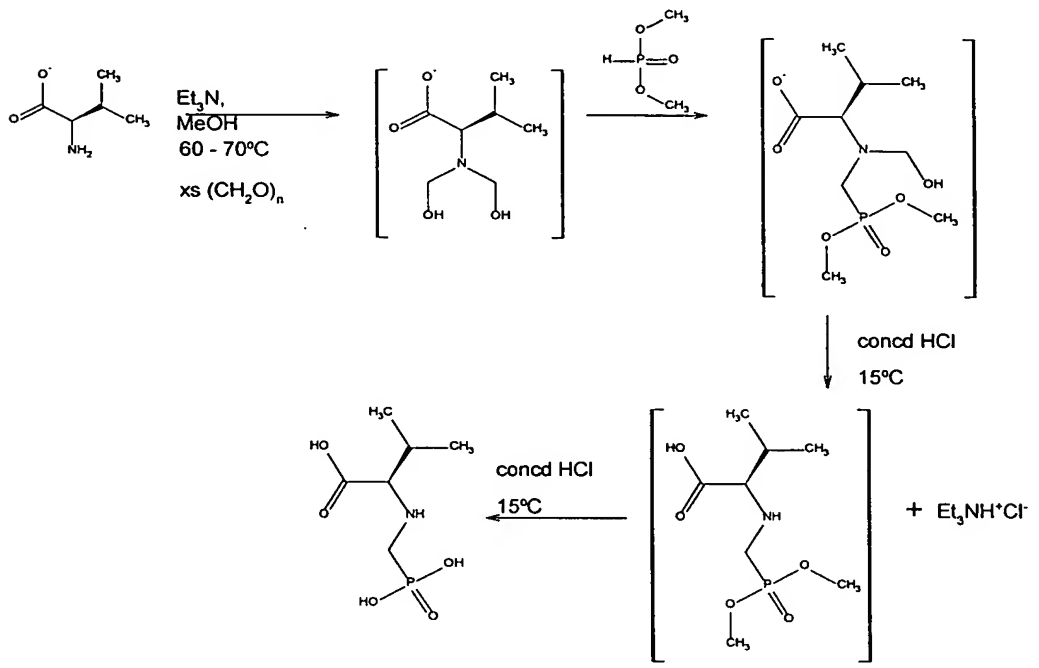
This assay was performed to investigate the efficacy of compounds in inhibiting larval growth. Media was prepared in an identical manner to that described above, and 5ml was added to wells containing 500µl of test compound. Each compound was tested at 1.25, 2.5, 5 and 10mM final concentration. The inhibitor was mixed evenly through the media, then the mixture was allowed to set. The media containing inhibitor was then divided between five plastic ups and two neonatal larvae were placed on the media in each cup. Larvae were left undisturbed for five days at 25-27šC in a room with a 16/8 hour light/dark cycle. Controls, containing the solvent dimethyl sulfonoxide (DMSO) which was used for dissolving the inhibitor, were included in each assay. After 5 days all cups were transferred to -20šC and left overnight before removal and weighing of the larvae. Larval weights were compared between treated and control groups. The results were expressed as a % inhibition.

Table 2

Ex.	Simple Name	% inhibition	Systematic Name
C1	valine methylphosphonate	37.5	3-Methyl-2-(phosphonomethyl-amino)-butyric acid
C2	leucine methylphosphonate hydroxamic acid	40.3	[(1-Hydroxycarbamoyl-3-methyl-butylamino)-methyl]-phosphonic acid monomethyl ester
C3	phenylalanine-N-methyl phosphonyl hydroxamic acid	50.1	[(1-Hydroxycarbamoyl-2-phenyl-ethylamino)-methyl]-phosphonic acid monomethyl ester
C4	N-methylalanine	50.9	2-Methylamino-propionic acid
C5	phenylalanine-N methyl phosphonic acid	55.0	3-Phenyl-2-(phosphonomethyl-amino)-propionic acid
C6	N-methylalanine hydroxamic acid	56.1	N-Hydroxy-2-methylamino-propionamide
C7	alanine hydroxamic acid-N methylphosphonate half methyl ester	58.4	[(1-Hydroxycarbamoyl-ethylamino)-methyl]-phosphonic acid monomethyl ester
C8	leucine intermediate	64.8	4-(2-methylpropyl)-3-(dimethoxy-phosphonomethyl)-2,2-bis-trifluoromethyl-oxazolidin-5-one
C9	N-acetyl phenylalanine hydroxamic acid	65.3	2-Acetylamino-N-hydroxy-3-phenyl-propionamide
C10	threonine methyl phosphonate derivative	65.6	2-[(Dimethoxy-phosphorylmethyl)-amino]-3-hydroxy-butyric acid methyl ester
C11	phenylalanine methyl phosphonic acid intermediate	70.8	4-Benzyl-3-bromomethyl-2,2-bis-trifluoromethyl-oxazolidin-5-one
C12	valine N,N di-methyl phosphonate derivative	72.0	2-[Bis-(dimethoxy-phosphorylmethyl)-amino]-3-methyl-butyric acid methyl ester
C13	phenylalanine hydroxamate intermediate	73.3	4-Benzyl-3-methyl-2,2-bis-trifluoromethyl-oxazolidin-5-one
C14	valine N-methyl phosphonate hydroxamic acid	75.6	[(1-Hydroxycarbamoyl-2-methyl-propylamino)-methyl]-phosphonic acid
C15	N-methylisoleucine	75.6	3-Methyl-2-methylamino-pentanoic acid
C16	leucine methylphosphonic acid hydroxamate	75.7	[(1-Hydroxycarbamoyl-3-methyl-butylamino)-methyl]-phosphonic acid
C17	valine derivative	79.7	2-Amino-1-(2-benzyloxymethyl-pyrrolidin-1-yl)-3-methyl-butan-1-one

Example 18

N-Phosphonomethyl-L-valine may also be prepared from (L)-valine by Mannich reaction according to the method of Scheme 3 shown below. This method is particularly suitable for larger scale preparations.



Scheme 3

It is to be understood that the invention herein above is susceptible to variations, modifications, and/or additions other than those specifically described and that the invention includes all such variations, modifications and/or additions which fall within the spirit or scope of the above description.

Example 19

Field evaluation of valine N-methyl phosphonate (vmpa) for control of *Helicoverpa* spp in cotton.

Objective: To evaluate the efficacy and crop safety of vmpa for control of *Helicoverpa* spp in a commercial cotton crop.

Location: Narrabri, NSW, Australia.

Dipel SC (Valent Corp, 4.0L/Ha)

Untreated control

Methodology:

Treatments were applied with a hand held gas operated boom incorporating three hollow cone nozzles/row. Output of the boom was approximately 140L/Ha. Trial sites were not sprayed for other pests such as two spotted mite or aphids. Plot size was 2 rows wide by 10m long, with each treatment replicated four times. The length of the buffer zone between treatments was 1.5m.

Assessments of Helicoverpa control were made by assessing larval number and developmental stage pre-spray and on days 3,7 and 10 after treatment. At the same time assessments of damage to the plants by the insects was assessed as the number of damaged 'squares'/metre of row. Observations for apparent phytotoxicity of the treatments were also made. The commercial insecticide Dipel (an Abbott BT formulation containing BT Kurstaki) was used as a positive control. Untreated plots (designated UTC) were retained to assess insect activity and or phytotoxicity of the treatments.

Results and Discussion

Results of the assessments of larval damage made at days 3 and 7 after treatment are shown in Table 1. Insect activity was extremely high during the trial (shown by high insect numbers and significant plant damage in the UTC plots). Phytotoxicity was not evident as a result of any of the insecticide treatments

Table 1: Number of larvae per metre of row

	Treatment	Rate	Pre	3 DAT	% efficacy day 0 - 3	7 DAT	% efficacy day 0 – 7
3	ValMPa	50 mm	11.5	7.5	***43.7***	12.6	***42.1***
4	ValMPa	25 mm	9.5	7.15	***35.0***	13.3	***26.4***
8	Dipel	4 L/ha	8.25	6	***37.2***	7.4	***52.8***
10	UTC		12	13.9	-	22.8	-

Table 2: No. of Damaged Squares Per Metre

Treatment	Rate	Pre	3 DAT	% efficacy day 0-3	7 DAT	% efficacy day 0-7
ValMPa	50 mm	3.0	3.8	***42.6***	8.0	***17.6***
ValMPa	25 mm	4.3	5.0	***45.9***	8.6	***37.3***
Dipel	4 L/ha	3.0	4.1	***36.8***	6.6	***31.7***
UTC		4.3	9.3	-	13.8	-

Heavy rain fall was recorded on the trial site at 5 DAT. The vmpa in this trial was in aqueous presentation and hence would not be expected to demonstrate significant efffectiveness after the rain. The results apparent at 3DAT and to a lesser extent at 7DAT indicated vmpa was as effective in control if helicoverpa as Dipel.

It is to be understood that the invention herein above is susceptible to variations, modifications, and/or additions other than those specifically described and that the invention includes all such variations, modifications and/or additions which fall within the spirit or scope

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